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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. ~~32~~ 55

Serial Number: 08/219200
Filing Date: 3/29/94
Appellant(s): Linsley et al.

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Sarah B. Adriano
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's Brief on Appeal, filed 9/15/98 (Paper No. 30).

The text of those sections of Title 35 U.S.Code not included in this appeal can be found in previous Office Actions herein.

(1) **Real Party of Interest.**

A statement identifying the real party of interest in contained in the Brief.

(2) **Related Appeals and Interferences Identified.**

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) **Status of Claims.**

The statement of the status of claims contained in the Brief is correct.

This appeal involves claims 79-94.

(4) **Status of Amendments After Final.**

Appellant's statement that the Supplemental Amendment, filed concurrently with the Appeal Brief on 9/15/98 (Paper No. 31), has not been acted on by the Examiner is acknowledged.

Appellant's Supplemental Amendment, filed 9/15/98 (Paper No. 31), has been entered.

(5) **Summary of Invention.**

The summary of invention contained in the Brief is correct.

(6) **Issues.**

The appellant's statement of the issues in the Brief is correct.

(7) **Grouping of Claims.**

Appellant's brief includes a statement that claims 79-94 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) **Claims Appealed.**

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(9) **Art of Record.**

The following is a listing of the art of record relied upon in the rejection of claims under appeal.

A) Blazar et al., J. Immunol. 157: 3250-3259 (1996).
B) Freeman et al., J. Immunol. 143: 2714-2722 (1989).
C) Kahan, Cur. Opin. Immunol. 4: 553-560 (1992).
D) Lenschow et al., Science 257: 789-792 (1992)
E) Perrin et al., J. Neuroimmunol. 65: 31-39 (1996).
F) Yi-qun et al., Intl. Immunol. 8: 37-44 (1996)

(10) **Grounds of Rejection.**

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 79-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as adhesion-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting cognate T:B interaction s with anti-CD28 antibodies and anti-B7 antibodies provides the basis for employing CD28Ig and B7Ig fusion proteins (CD28 immunoglobulin fusion protein and B7 immunoglobulin fusion protein)((see page 72, paragraph 1 of the instant specification). It is noted that B7Ig inhibited CD28-mediated adhesion in vitro to a lesser degree than the CD28-specific antibody 9.3 and that CD28Ig did not inhibit said in vitro adhesion (see page 64 of the instant specification). In addition, B7Ig in solution showed a modest enhancement of proliferation of T cells in vitro even though anti-CD28

antibody 9.3 was effective (page 65 of the instant specification). There is no objective evidence that CD28Ig was tested in this in vitro system or other experimental in vitro or in vivo systems that would be predictive of the therapeutic methods encompassed by the claims. There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed methods to inhibit T cell proliferation or to prevent binding of CD28 receptor to B7 antigen, commensurate in scope with the therapeutic methods encompassed by the claimed invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2).

Blazar et al. (J. Immunol., 1996) discloses that issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10.

Blazar et al. (J. Immunol., 1996) discloses that anti-CD80 or anti-CD86 antibodies were ineffective in preventing T cell CD8-mediated GVHD lethality; that each antibodies was partially effective in CD4-mediated GVHD lethality and that the combination of anti-CD80 and anti-CD86 antibodies were effective in preventing GVHD lethality in murine experimental models (see entire document, including the Abstract)

Similarly, Perrin et al. (J. Neuroimmunol, 1996) discloses that in contrast to the effective treatment of disease with CTLA-4 Ig; anti-CD80 (B7-1) attenuated the first clinical disease episode but not the relapse, anti-CD86 (B7-2) had no significant effect on the course of disease, and the combined treatment with anti-CD80 plus anti-CD86 resulted in the exacerbation of disease (see entire document). It is also noted that CTLA-4 Ig had a marked but incomplete therapeutic effect in the EAE model.

In addition, Yi-qun et al. (Intl. Immunol., 1996) discloses that their findings have a number of important implications for therapeutic approaches (see entire document, particularly Discussion, last paragraph). It is clear that inhibition of T cell response to soluble antigens will require the blocking of both B7-2 and B7-1 to be effective. More, important it is unlikely that ongoing T cell response will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases.

Therefore, it is acknowledged that the administration of the CD28:B7 inhibitor CTLA-4 Ig can result in immunosuppression as observed in several model systems. However even in these systems; the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention.

In contrast to the role and avidity that the CD28:B7 inhibitor CTLA-4 Ig appears to have in vivo, there is insufficient objective evidence in the instant application that either the claimed B7Ig or CD28Ig fusion proteins alone can inhibit T cell function or interactions in vivo and the objective evidence above would indicate that neither would be predicted to inhibit in vivo function or interactions.

Immunosuppression and inhibition of leukocyte interactions and functions are much easier to achieve under controlled in vitro conditions that experienced in the human immunoregulatory diseases targeted by the claimed invention. Further, in animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Therefore, it should be noted that although the animal models validate concepts based on studies of human disease, such studies are limited to the acute as opposed to chronic nature of the disease. Immunosuppression is much easier to achieve under such controlled conditions to defined antigens in mice than that experienced in the human immunoregulatory diseases targeted by the claimed invention.

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by B7 Ig or CD28 Ig fusion proteins. The specification does not teach how to extrapolate data obtained from the disclosed in vitro assays based upon the claimed B7 Ig or CD28 Ig fusion proteins or from other CD28:B7 inhibitors such as antibodies (e.g. anti-B7 antibodies) or CTLA-4 Ig to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention. Again, it is noted that the claimed B7Ig inhibited CD28-mediated adhesion in vitro to a lesser degree than the CD28-specific antibody 9.3 and that the claimed CD28Ig did not inhibit said in vitro adhesion (see page 64 of the instant specification). In addition, B7Ig in solution showed a modest enhancement of proliferation of T cells in vitro even though anti-CD28 antibody 9.3 was effective (page 65 of the instant specification). There is no objective evidence that CD28Ig was tested in this in vitro system or other experimental in vitro or in vivo systems that would be predictive of the therapeutic methods encompassed by the claims. Therefore, there is insufficient objective evidence that accurately reflects the relative efficacy of the claimed method or therapeutic strategies to inhibit T cell proliferation or to prevent binding of CD28 receptor to B7 antigen, commensurate in scope and encompassed by the claimed methods.

Furthermore, the disclosed uses encompassed by the claimed methods are the inhibition of transplant rejection, GVHD, autoimmunity, infectious disease and neoplasia (see Uses In Vitro and In Vivo on pages 23-29 of the instant specification). Based upon the objective evidence disclosed in the instant specification and in the art, the skilled artisan could not predict the efficacy or enablement of B7 Ig or CD28 Ig fusion proteins to inhibit T cell function or interactions in the targeted diseases or patients encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting T cell function and interactions.

Rejection Under 35 U.S.C. § 112, First and Second Paragraphs

Claims 79-94 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite in the recitation of "B7" and "containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 antigen " because their characteristics are ambiguous and not defined. The compounds of interest are defined by an arbitrary protein name (i.e. B7). While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein and variants thereof. Others in the field may isolate the same protein and give such an entirely different name. Also, B7 can refer to a number of distinct proteins expressed on various tissues and in various animal species. Applicant should particularly point out and distinctly claim the B7 antigen by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compounds are made up of. This language is vague and indefinite since it can encompass many different proteins and it is not apparent which particular antigen is being referred to.

Furthermore, the recitation of the certain amino acid sequences are ambiguous and confusing since it is unclear as to what is the base amino acid sequence being relied upon.

While the specification, while being enabling for a B7 protein as sequenced by Freeman et al. (J. Immunol., 1989 (page 6, paragraph 1 of the instant specification), does not reasonably provide enablement for any B7 protein and, in turn, for any B7 fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not appear to specifically define the metes and bounds of "B7" or "B7 antigen". As such, this term cannot be considered to be limited to the specific B7 antigen disclosed in the specification. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable identification of any other B7 antigen meeting the structural or functional limitations of the instant invention and it is deemed to constitute undue experimentation to determine them. Further, it is not the intention of the instant disclosure to be drawn to any B7 antigen other than the B7 antigen as defined by the Freeman et al. (J. Immunol., 1989) . Applicant has enabled only this B7 antigen and, in turn, only those sequences and extracellular domains derived from said B7 antigen. The disclosure is not commensurate in scope with the breadth of the claims.

Appellant has been invited to amend the claimed limitations to include a SEQ ID NO. for the claimed B7 antigen.

(11) **Response to Argument**

Rejection Under 35 U.S.C. § 112, First Paragraph

Appellant's arguments, filed 9/15/98 (Paper No. 30), have been fully considered but have not been convincing essentially for the reasons of record.

Appellant argues that one is not required to enable any more than what is claimed and that the Office is improperly imposing a requirement that appellant demonstrate commercial success to meet the enablement requirement. Appellant argues that there is sufficient teachings in the specification to meet the claimed methods. Appellant asserts that all that is required is to teach how to make and use the claimed invention. Further, appellant argues that the claims are not directed to methods of treating a patient.

In contrast to appellant's arguments, no such requirement of commercial success has been indicated.

In contrast to appellant's assertions, it is clear that the disclosed uses encompassed by the claimed methods are the inhibition of transplant rejection, GVHD, autoimmunity, infectious disease and neoplasia (see Uses In Vitro and In Vivo on pages 23-29 of the instant specification). Based upon the objective evidence disclosed in the instant specification and in the art, the skilled artisan would not predict the efficacy or enablement of the claimed B7 Ig or CD28 Ig fusion proteins to inhibit T cell function or interactions encompassed by or commensurate in scope with the claimed methods, including the disclosed targeted diseases or patients.

Also, appellant acknowledges that anti-CD28 antibodies may exert stimulatory or inhibitory effects on T cells and asserts that B7Ig would act to stimulate of inhibit T cells in a similar manner. Therefore, appellant acknowledges that the claimed B7Ig has both stimulatory and inhibitory properties depending on conditions, which would lend to the unpredictability of administering said B7Ig fusion protein in vivo to achieve the claimed inhibitory methods, commensurate in scope with the claimed invention.

Further, appellant argues that CD28Ig would prevent endogenous stimulation of CD28 by B7 positive cells and interfere with T cell responses accordingly. However, appellant has not provide sufficient objective evidence to support this assertion, particularly in view of the absence of inhibitory activity by CD28Ig in vitro, as disclosed in the instant specification.

In contrast to appellant's assertions, the following observations have been noted with the claimed fusion proteins in vitro. Appellant has relied upon page 71, paragraphs 1-2 of the instant specification which discloses that monoclonal antibodies 9.3 (anti-CD28) and BB-1 (anti-B7) block T_h cell-induced Ig productions by B cells. However, the instant methods rely upon the use of B7Ig and CD28Ig rather than anti-CD28 and anti-B7 antibodies. B7Ig inhibited CD28-mediated adhesion in vitro to a lesser degree than the CD28-specific antibody 9.3 and that CD28Ig did not inhibit said in vitro adhesion (see page 64 of the instant specification). In addition, B7Ig in solution showed a modest enhancement of proliferation of T cells in vitro even though anti-CD28 antibody 9.3 was effective (page 65 of the instant specification). There is no objective evidence that CD28Ig was tested in this in vitro system or other experimental in vitro or in vivo systems that would be predictive of the therapeutic methods encompassed by the claims. There is insufficient objective evidence that accurately reflects the relative efficacy or enablement of the claimed methods to inhibit T cell proliferation or to prevent binding of CD28 receptor to B7 antigen, commensurate in scope with the therapeutic methods encompassed by the instant invention.

In contrast to appellant's assertions, appellant has not addressed the objective evidence including appellant's own observations concerning the predictability of B7Ig or CD28Ig to accomplish the inhibitory endpoints, encompassed by the claimed methods.

Appellant relies upon the observations of Lenschow et al. (Science,1992) to show that blocking CD28:B7 interactions results in manipulating the immune system. However, this reference relies upon the use of the B7:CD28 inhibitor CTLA4Ig (CTLA4 immunoglobulin fusion protein) rather than the use of the claimed CD28Ig or B7Ig fusion proteins. The rejection of record has relied upon the observations of Blazar et al. (J. Immunol., 1996), Perrin et al. (J. Neuroimmunol, 1996) and Yi-qun et al. (Intl. Immunol., 1996) as well as scientific reasoning to indicate the differences between the observations associated with the high affinity/avidity CTLA4Ig and the extrapolation of limited, if any, inhibitory properties of the instant B7Ig and CD28Ig in the instant methods. For example, the administration of CTLA-4 Ig can result in immunosuppression as observed in several model systems, however even in these systems the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention. For the reasons of record and set forth herein, including applicant's own disclosure and the art; soluble B7 and CD28 fusion proteins have not met the limitations of the instant methods. Issues such as tissue distribution, half-life, affinity and avidity obtained with various CD28:B7-specific reagents on altering in vivo immune responses should be interpreted in light of the type of reagent infused (Blazar et al., J. Immunol., 1996; see page 3257, column 2, paragraph 10).

Appellant's arguments, concerning the previous rejections based on the utility and enablement of B7 and CD28 immunoglobulin fusion proteins are acknowledged. As pointed out previously and contrary to appellant's assertion, an examiner is not prohibited from making a new grounds of rejection provided it is warranted during the prosecution of a patent application. Appellant has had the options of appealing or petitioning the patent application.

Appellant's reliance upon the NIH-approved protocols involving the use of CD28 (Exhibit 2) is not found convincing in that these protocols address gene therapy, which involve distinct ingredients, process steps and endpoints that those encompassed by the instant claimed methods. For example, the gene therapy methods encompass increasing or stimulating an immune response rather than inhibiting T cells responses as encompassed by the instant methods.

In contrast to appellant's assertions that no undue experimentation would be required to meet the claimed invention; the rejection of record has relied upon the same Forman Factors relied upon by appellant to support appellant's assertions to indicate the lack of predictability of using the claimed B7Ig and CD28Ig fusion proteins in the claimed methods and commensurate in scope with the claimed invention.

In contrast to appellant's reliance on these limited in vitro experimental observations wherein soluble B7 exhibited limited ability to inhibit CD28-mediated adhesion and soluble CD28Ig exhibited no ability to inhibit CD28-mediated adhesion; no objective evidence was relied upon to use soluble B7 or soluble CD28 to inhibit T cell proliferation, to inhibit binding of CD28 positive T cell to B7 positive B cells , to inhibit CD28 positive T cell response, to inhibit the binding of B7 positive B cells to CD28 positive T cells, commensurate in scope with the claimed methods, encompassing the inhibition of transplant rejection, GVHD, autoimmunity (e.g. IDDM, myasthenia gravis, rheumatoid arthritis and SLE on page 72 paragraph 1 of the instant specification), infectious disease and neoplasia (see Uses In Vitro and In Vivo on pages 23-29).

In contrast to the role that the CD28-B7 inhibitor CTLA-4 Ig appears to have in vivo, there is insufficient objective evidence in the instant application that either B7Ig or CD28Ig fusion protein alone can inhibit T cell function or interactions in vivo and the objective evidence of record would indicate that neither would be predicted to inhibit in vivo function or interactions.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting T cell function and interactions by administering or providing soluble B7 and CD28 fusion proteins, commensurate in scope with the claimed methods.

Appellant's arguments are not found persuasive.

Rejection Under 35 U.S.C. § 112, First and Second Paragraphs

Appellant's arguments, filed 9/15/98 (Paper No. 30), have been fully considered but have not been convincing essentially for the reasons of record.

Appellant argues that the term "B7" is definite and that the entire nucleotide sequence for one B7 protein has been provided and described the functions which other members of the class of proteins provided by the invention would have to have.

Appellant's reliance on B7 as disclosed by Freeman et al. (J. Immunol., 1989) is acknowledged. However the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

Appellant has argued that the specification discloses that the defining characteristic of B7, namely that it is the B cell ligand for CD28 (specification at page 43) and that B7 is the single art accepted term for this molecule as first described in Freeman et al., J. Immunol, 143: 2741-2722 (1989).

Appellant relies upon complementary and redundant assays for B7 molecules encompassed by the claims for those molecules that effect cellular processes in their capacity to act as a ligand for the CD28 molecule on T cell. In contrast to appellant's assertions for the enablement of a wide variety of molecules that bind CD28, there is sufficient guidance and direction as to the B7 molecule disclosed by Freeman et al. (J. Immunol, 1989) in the application as filed.

In contrast to applicant's assertions that applicant need not disclose every known B7 molecules or that it would not have been undue experimentation to determine other members of a class of B7 binding molecules; the instant specification did not provide direction or guidance as to a family of B7 molecules, but rather relied upon the B7 molecule disclosed by Freeman et al. (See page 11, paragraph 1 of the instant specification).

In contrast to appellant's arguments that B7 is the single art accepted for this molecule, B7 is a family of molecules including B7-1/CD80 and B7-2/CD86 (for example, see Yi qun et al. International Immunology, 1996, Introduction). Furthermore, it is noted that the members of the B7 family have different structures and properties. For example, Yi qun et al. (International Immunology, 1996, Introduction) discloses that upon testing human B cells are B7-negative and upon activation, B7-2 appears more rapidly than B7-1. Also, human peripheral blood monocytes constitutively express B7-2, where B7-1 is only expressed on monocytes after activation with IFN-γ or GM-CSF. Peripheral blood dendritic cells are CD80-negative and only express CD86 weakly, but both molecules are rapidly induced during culture. Therefore, B7 represents a family of distinct molecules which expression differs between cell types and cell activation.

In contrast to appellant's assertions tht B7 is well-defined on pages 19-29 of the specification, there is no recognition of the complexity of the B7 family of molecules, as evidenced by Yi qun et al. (International Immunology, 1996; see Introduction).

Again, the recitation of the certain amino acid sequences are ambiguous and confusing since it is unclear as to what is the base amino acid sequence being relied upon. Again, appellant has enabled only the B7 antigen disclosed in Freeman et al. (J. Immunol., 1989) and, in turn, only those sequences and extracellular domains derived from said B7 antigen. Again, appellant has been invited to amend the claimed limitations to include a SEQ ID NO. for the B7 antigen.

Appellant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

Appellant's arguments are not found persuasive.

(12) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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